Patent
Attorney's Docket No. 016800-111

#34 Plunkett 12/19/00 1063

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
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Yann MAHE et al.	)	Group Art Unit: 1642
	)	
Application No.: 08/716,531	)	Examiner: S. Huff
	)	
Filed: September 19, 1996	)	Appeal No. Unassigned
	)	
For: PHARMACEUTICAL/COSMETIC COMPOSITIONS COMPRISING THE LYSINE-D-PROLINE-VALINE TRI-PEPTIDE	)	

APPELLANTS' REPLY TO THE EXAMINER'S ANSWER

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noted SJH 1/25/01

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Assistant Commissioner for Patents
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Sir:

Pursuant to 37 C.F.R. §1.193(b)(1) Appellants file this Reply to the Examiner's Answer (Paper No. 32) to their Appeal Brief, which was mailed on October 10, 2000. **Two copies of this brief are submitted.**

The Examiner has acknowledged that Appellants' statements in their Appeal Brief regarding the Status of the Claims and Amendments are correct, and has agreed that the Summaries of the Invention and Issues stated in the Brief are correct.

I. BRIEF SUMMARY OF THE INVENTION

The invention of the present application is a method of treating inflammation comprising administering a therapeutically effective amount of peptide comprising the peptide sequence lysine-D-proline-valine. The lysine and valine residues of the tri-peptide may be either the levorotatory (L) or dextrorotatory (D) optical isomers; the proline moiety is the dextrorotatory isomer (D-Pro.).

In preferred embodiments, the tri-peptide of the composition comprises D-Lys-D-Pro-D-Val, D-Lys-D-Pro-L-Val, L-Lys-D-Pro-D-Val or L-Lys-D-Pro-L-Val. It may include protecting groups to enhance its stability. The claimed method comprises administering a composition containing the tri-peptide by applying it to the skin, scalp and/or mucous membranes of a mammalian organism to alleviate inflammation.

The prior art available as of the filing date of the application taught that the peptides of the composition used in the method of treating inflammation in the present invention did not

exhibit anti-inflammatory activity. While it had been proposed that administration of derivatives of α-MSH, particularly the peptide Lys-Pro-Val, could be used to treat inflammation (U.S. Patent Nos. 5,028,592 and 5,157,023), the proline present in those peptides was L-Pro. Significantly, it was understood that peptides containing D-Pro were not effective for the treatment of inflammation. (Hiltz et al, *Peptides* 12 (1991), pp. 767-771 at 767.) Consequently, Appellants' invention, a method of treatment for inflammation using a composition containing the tri-peptide Lys-D-Pro-Val, was completely unexpected. The anti-inflammatory activity of the tri-peptide is shown by the results contained in the Examples of the subject application. Examples 1-4 of the application demonstrate that the peptide inhibits the production of the pro-inflammatory cytokines (IL-1α, IL-1R1, IL-1R2) in patients suffering from an inflammatory condition.

II. REPLY TO THE EXAMINER'S ANSWER

A. The Anticipation Rejection Based on Ferreira Is Improper

Claims 1-3 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ferreira et al. Appellants assert that this rejection is improper and asks that it be reversed.

Ferreira et al. disclose that the tri-peptide K(D)PV (Lys-D-Pro-Val when written using three letter amino acid abbreviations) and its amides and salts are analgesics, compounds that relieve pain. (U.S. Patent No. 5,389,615, col. 2, lines 46-52, lines 59-61, col. 3, lines 53-59, col. 4, line 59 to col. 5, line 3, the Examples and the claims.)

The Examiner relies on Ferreira et al. to equate pain and inflammation. (Examiner ' s Answer at 10.) It is argued that Ferreira et al.' s discussion of the two proteins known as

Interleukin-1 (IL-1) and their role in the release of prostaglandins, which sensitize pain receptors in man and in animals, equates pain and inflammation. Appellants respectfully disagree. Methods that are effective for treating pain are not necessarily methods that are effective for treating inflammation. Ferreira et al. contains no teachings whatsoever that the peptides used in the methods of the present invention are effective for treating inflammation. Ferreira ' s discussion of the inflammatory proteins IL-1 and their role in the release of prostaglandins, taken together with its conclusion that the peptides of this patent may be used as analgesics, is an indication that these inventors distinguish pain and inflammation.

It is asserted that the comparison of the analgesic activity of the tri-peptide used in the compositions of the present invention to the activity of indomethacin, an anti-inflammatory agent, supports the argument that pain and inflammation are equivalent. Again, Appellants respectfully disagree. The 2001 Physicians' Desk Reference describes indomethacin (Indocin®) as a non-steroidal drug with anti-inflammatory, antipyretic and analgesic properties. (A copy is attached.) Thus, the makers of indomethacin distinguish its anti-inflammatory and analgesic (anti-pain) properties. Example 10 of the Ferreira reference, comparing the effect of the peptide Lys-D-Pro-Thr and indomethacin on hyperalgesia evoked by ip injections of acetic acid and Iloprost, nowhere asserts or even suggests that the tri-peptide can be used in a method for treating inflammation. Moreover, it provides no indication that Ferreira relied on or even recognized the anti-inflammatory properties of indomethacin in the reported study. The use of indomethacin as a control analgesic compound in this study of the effects of the tri-peptide on hyperalgesia (pain) does not show that pain and inflammation are equivalent.

Appellants have relied on relevant pages from Chapter 12 of a book entitled, Drugs to Suppress Inflammatory and Immune Reactions to show that the usefulness of a specific compound for treating inflammation cannot be reliably predicted from a demonstration that the compound is useful in a method for treating pain. The Examiner's observation that 16 of 18 drugs listed in Table 12.1 of that reference treated both inflammation and pain does not demonstrate that a method of treating pain is equivalent to a method of treating inflammation, or that a method of treating pain anticipates a method of treating inflammation.

The Hoffman and Schmelz abstract discussed by Appellants is acknowledged in the Examiner's Answer to show that hyperalgesia and inflammation may be caused by different stimuli. Appellants have acknowledged that pain may accompany inflammation. However, the fact that a compound has analgesic properties does not allow a conclusion that it will also have anti-inflammation properties.

"Anticipation under Section 102 can be found only if a reference shows exactly what is claimed." *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 U.S.P.Q. 773 (Fed. Cir. 1985). Here, Ferreira does not show what is claimed in claims 1-3 of the appealed application. Accordingly, Appellants respectfully ask that the rejection of these claims under Section 102(b) be reversed.

B. The Anticipation Rejection Based on Oluyomi et al. Is Improper

Oluyomi et al. also fails to show what is claimed in the appealed application. This reference reports the results of tests of a series of compounds, including Lys-D-Pro-Val, in two models of antinociception, or analgesia (anti-pain). They do not teach the use of the tri-

peptides of the claimed inventions in a method for treating inflammation. Again, Appellants respectfully ask that the rejection of claims 1-3 under Section 102(b) be reversed.

Appellants are not ignoring the data presented in the Oluyomi reference as alleged in the Examiner's Answer. They are, however, interpreting the reference based on the understanding of one of skill in the art relevant to the claimed invention. Appellents do not dispute that inflammation may be accompanied by pain. However, they do disagree with the Examiner's interpretation of the statements cited from the Oluyomi reference. First, the statement on page 131 refers generally to peptide analogues containing the dipeptide Lys-Pro, not to the specific tri-peptide Lys-D-Pro-Val used in the claimed methods of the present application. Second, the reference refers to the control of **pain,** not to the control of inflammation. The Examiner's interpretation of this sentence is not supported by the statement made in the reference. Moreover, the statement does not transform the disclosure of Oluyomi into an anticipating reference.

The Examiner's citation of the sentence on page 136 also does not support the contention that pain is equivalent to inflammation. The sentence reads, "In the present study, however, the ability of these peptides to be antinocieptive in the abdominal constriction test, **may be** as a result of their ability to inhibit the release of prostaglandins or other inflammatory substances." First, the term "antinocieptive" refers to analgesia or anti-pain. Second, the use of the term "may be," which is consistent with disclosure of the reference, indicates that the author is speculating here. Finally, there is no indication as to which peptides this speculation applies.

The last citation, to page 137 of Oluyomi is not complete. The entire sentence reads, "This confirms the peripheral anti-inflammatory activity of this peptide as reported by Hiltz and Lipton (1989) and its analogues (Hiltz et al., 1991). Significantly, in the next paragraph Oluyomi states

> L-Pro^{12} of α-MSH is thought to be important in the anti-inflammatory response to picryl chloride injection (Hiltz et al., 1991) as Lys-D-Pro-Thr was found to be ineffective on swelling, a major characteristic of inflammation. Hiltz et al. (1991) however found that altering the stereo-chemical make-up of their tripeptides via D-substitution with D-amino acids increased stability, potency and duration of action but loss of anti-inflammatory activity.

Hiltz et al. reported that "Ac-[D-Pro^{12}]α-MSH (11-13) NH_2 had no significant anti-inflammatory activity." This loss of activity was attributed to the substitution of D-Pro^{12} for L-Pro.^{12} Nowhere does Oluyomi dispute the findings of Hiltz et al., nor does he suggest that the findings of his own work dispute the finding that altering the stereo-chemical make-up of the tri-peptide via substitution with D-amino acids increases the loss of anti-inflammatory activity. The disclosure of Oluyomi is not contrary to the teachings of Hiltz (1991) that Ac-Lys-D-Pro-Val-NH_2 was inactive in the anti-inflammatory assay. The teachings of the present application are based on the surprising discovery that the peptides could be administered in a therapeutically effective amount in a method for treating inflammation. Appellants respectfully ask that the Section 102(b) rejection of claims 1-3 be reversed as the reference does not teach the method of treating inflammation that is the invention of the present application.

C. The Rejection of Claims 1-11 and 16-19 As Being Obvious Over Ferreira and/or Oluyomi Are Improper

Claims 4, 7-10 and 18 stand rejected under Section 103(a) as being obvious in view of Ferreira et al. for the reasons stated in the rejection of claims 1-3 under Section 102(b). However, Appellant has shown above that Ferreira et al. does not teach or even suggest the method of the present invention, particularly the embodiment of claim 4, directed to the method of treating inflammation where at least one peptide of the composition is D-Lys-D-Pro-D-Val. Likewise, there is nothing in the teachings of Ferreira to even suggest the use of specific concentrations of the tri-peptide in the composition of the method for treating inflammation, the embodiments of claims 7-10. Ferreira does not teach or suggest a method of treating inflammation comprising administration of a composition comprising an effective anti-inflammatory amount of the tri-peptide and an effective amount of a glucocorticoid, vitamin D or derivative thereof or a non-steroidal anti-inflammatory agent. Since Ferreria et al. does not disclose or suggest the inventions of claims 4, 7-10 and 18, Appellants respectfully request that this Section 103(a) rejection be reversed.

Claims 5-6 and 19 stand rejected as being obvious over Ferreira et al. in view of Lipton and Oluyomi. Ferreira and Oluyomi are relied on as teaching a method of treating pain which is incorrectly equated with a method of treating inflammation. Lipton is cited to show that the use of protection groups to increase stability of peptides was known in the art. It does not teach methods of treating inflammation using compositions comprising the specific peptides disclosed in the present application. Since Ferreira et al. do not disclose or suggest the inventions of claims 5-6 and 19, and Oluyomi teaches away from the claimed method of

the present application, the additional citation of Lipton does not render the claims obvious. Appellants respectfully ask that the rejection of claims 5-6 and 19 be reversed.

Claims 1-11 and 16-19 stand rejected as being obvious over Ferreira et al., in view of Nordlund, Lipton, Remington's Pharmaceutical Science Chapters 87 and 92 and Oluyomi et al. Nordlund and the pages from Remington's are cited to show only that topical administration of an α-MSH composition is known in the art. Because Ferreira et al. and Oluyomi et al. do not disclose the method of the present application, the additional citation of Nordlund and Remington does not make the method obvious. Applicants respectfully request the rejection of claims 1-11 and 16-19 be reversed.

III. CONCLUSION

In conclusion, Appellants respectfully request that the prior art rejections be reversed. Taken alone or in combination, the cited art fails to teach or suggest a method of treatment comprising the administration of a pharmaceutical/cosmetic composition comprising an anti-inflammatory effective amount of a tri-Lys-D-Pro-Val. Rather, the prior art only suggests the antinociceptive (anti-pain) activity of this peptide and actually teaches against its use as an

anti-inflammatory given the prior belief that the L form of proline was essential on inflammatory activity.

Respectfully submitted,

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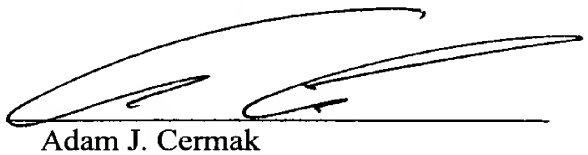
By: 

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